From: [redacted]
Sent: Tuesday, May 11, 2004 2:18 PM
To: Shelby, Michael (NIH/NIEHS)
Subject: acrylamide BMDs

Dear Mike: I am sorry to be sending this to you so late in the game, and if I have broken the rules regarding comments to reports please forgive me.

There is one aspect of the draft acrylamide report that bothered me; I had thought that it would be flaggged by one of the public commentors, but alas it was not. That is the BMD calculation for the resorption rate in the Tyl study, which is given in the report as "<<1 mg/kg". Granted, the report makes statements that this value is probably unreliable, but even so, it's a concern.

After reading that part of the report several times, and doing my own calculations using EPA's BMD software (and talking to Tony), I figured out why the BMD for resorptions is so low: it's based on a 10% relative change from controls, which is not appropriate, at least in my opinion, from a biological or statistical POV. Historical control data for resorption rates in rats run in the 3-15% range (data from the MARTA compilation) with a mean of 5-6%. The control mean in the Tyl study happens to be 3%. A 10% relative change means that the BMD is the dose that would give a 3.3% resorption rate, lower than the historical mean, and also well within the range of the standard deviation of this value in the Tyl study, which was +/- 5.6%. That, combined with the fact that resoprtion rate has an inherently high variability (the SD being bigger than the mean is not uncommon for resorptions) fully explains why the BMDL th! at was calcualted is so low.

As I said, I went back to the data and calculated BMDs and BMDLs using what I believe are still conservative, but more defensible criteria. (Data were plotted using the linear model.) First, I chose an absolute increase of 3%: in a typical Segment 2 study with 20 animals per group, the statistical power is such that one should be able to statistically detect a doubling in the resorption rate. The Tyl study doesn't have the same number per group, so power may be less. In any case, choosing a 3% absolute increase over the control value of 3% seems reasonable. In that case, the BMD is approximately 5 mg/kg/d, with a BMDL of 3.7 mg/kg/day. I also chose two other benchmark levels that I thought would be reasonable and conservative: 0.5 of a SD, and 0.1 of a SD. Because of the variability in the data, it seems to me that basing the BMD as a fraction of the overall SD makes sense. The 0.5 SD standard! has been proposed several times inthe literature. I chose 0.1 SD simply because it strikes me as being very conservative. For the 0.5 SD, the BMD is 25 mg/kg/day and BMDL is 16.7, for the 0.1 SD the values are 4.85 and 3.34, respectively. So, even with an overly conservative standard, the BMDL is still in the range of the data.

I hope that you will be able to consider these thoughts as you work on the acrylamide report. I understand the desire to have a standard level for BMD, but in this case it doesn't fit the biology.

Regards, [redacted]